SODIUM SALTS OF 5-'4-'2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY!BENZYL!THIAZOLIDINE -2,4-DIONE

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of example 30 of EP 0,306,228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter also referred to as "Compound (I)").

International Patent Application, Publication Number WO94/05659 discloses certain salts of the compounds of EP 0,306,228. The preferred salt of WO94/05659 is the maleic acid salt.

It has now been discovered that Compound (I) forms a novel sodium salt (hereinafter also referred to as the "Sodium Salt").

The novel Sodium Salt is a stable, high melting crystalline material hence is suitable for bulk preparation and handling. The Sodium Salt is amenable to large scale pharmaceutical processing, especially in manufacturing processes which require or generate heat, for example milling, fluid bed drying, spray drying, hot melt processing and sterilisation by autoclaving.The novel salt can be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation. In addition the novel Sodium Salt is non-hygroscopic and shows good solid state stability, especially under humid conditions.

The novel Sodium Salt also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt, especially a non-hygroscopic sodium salt or solvate thereof.

In one favoured aspect, the Sodium Salt provides an infrared spectrum substantially in accordance with Figure 1.

In one favoured aspect, the Sodium Salt provides a Raman spectrum substantially in accordance with Figure 2.

In one favoured aspect, the Sodium Salt provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3.

In one favoured aspect, the Sodium Salt provides a Solid State ^{13}C NMR spectrum substantially in accordance with Figure 4.

In a preferred aspect, the invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt, or solvate thereof characterised in that it provides:

(i) an infrared spectrum substantially in accordance with Figure 1; and

(ii) a Raman spectrum substantially in accordance with Figure 2; and

(iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and

(iv) a Solid State ^{13}C NMR spectrum substantially in accordance with Figure 4.

Suitably the Sodium Salt has a melting point in the range of from 245 to 250°C, such as 246 to 249°C, for example 246°C or 249°C.

The present invention encompasses the Sodium Salt or solvate thereof isolated in pure form or when admixed with other materials. Thus in one aspect there is provided the Sodium Salt or solvate thereof in isolated form.

In a further aspect there is provided the Sodium Salt or solvate thereof in a purified form.

In yet a further aspect there is provided the Sodium Salt or solvate thereof in crystalline form.

Also, the invention provides the Sodium Salt or solvate thereof in a solid pharmaceutically acceptable form, such as a solid dosage form, especially when adapted for oral administration.

Moreover, the invention also provides the Sodium Salt or solvate thereof in a pharmaceutically acceptable form, especially in bulk form, such form being particularly capable of pharmaceutical processing, especially in manufacturing processes which require or generate heat, for example milling; for example heat-drying especially fluid-bed drying or a spray drying; for example hot melt processing; for example heat-sterilisation such as autoclaving.

Furthermore, the invention provides the Sodium Salt or solvate thereof in a pharmaceutically acceptable form, especially in bulk form.and especially in form having been processed in a manufacturing process requiring or generating heat, for example in a milled form; for example in heat-dried form, especially a fluid-bed dried form or a spray dried form; for example in a form having being hot melt processed; for example in a form having being heat-sterilised by such as autoclaving.

As indicated above the Sodium Salt of the invention is non-hygroscopic. The invention further includes non-hygroscopic or slightly hygroscopic pharmaceutically acceptable solvates, including hydrates, of the Sodium Salt.

The invention also provides a process for preparing the Sodium Salt or a solvate thereof, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]

thiazolidine-2,4-dione (Compound (I)) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a source of Sodium ion and thereafter, if required, a solvate of the resulting Sodium Salt is prepared; and the Sodium Salt or a solvate thereof is recovered.

A suitable reaction solvent is an alkanol, for example propan-2-ol, or an ether such as tetrahydrofuran, a hydrocarbon, such as toluene, a ketone, such as acetone, an ester, such as ethyl acetate, a nitrile such as acetonitrile, or a halogenated hydrocarbon such as dichloromethane, or water; or a mixture thereof.

Conveniently, the source of sodium ion is sodium hydroxide. The sodium hydroxide is preferably added as a solid or in solution, for example in water or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents.

The concentration of Compound (I) is preferably in the range 2 to 25% weight/volume, more preferably in the range 5 to 20%. The concentration of sodium hydroxide solutions are preferably in the range of 2 to 111% weight/volume.

The reaction is usually carried out at ambient temperature or at an elevated temperature, for example at 50-60°C or, at the reflux temperature of the solvent, although any convenient temperature that provides the required product may be employed.

Solvates, such as hydrates, of the Sodium Salt are prepared according to conventional procedures.

Recovery of the required compound generally comprises crystallisation from an appropriate solvent, conveniently the reaction solvent, usually assisted by cooling. For example, the Sodium Salt may be crystallised from an alcohol such as propan-2-ol, an ether such as tetrahydrofuran, or water, or a mixture thereof. An improved yield of the salt can be obtained by evaporation of some or all of the solvent or by crystallisation at elevated temperature followed by controlled cooling, optionally in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the product form.

Crystallisation can also be initiated by seeding with crystals of the Sodium Salt or a solvate thereof but this is not essential.

Compound (I) is prepared according to known procedures, such as those disclosed in EP 0,306,228 and WO94/05659. The disclosures of EP 0,306,228 and WO94/05659 are incorporated herein by reference.

Sodium hydroxide is a commercially available compound.

When used herein the term "T_{onset}" is generally determined by Differential Scanning Calorimetry and has a meaning generally understood in the art, as for example expressed in Pharmaceutical Thermal Analysis, Techniques and Applications", Ford and

Timmins, 1989 as "The temperature corresponding to the intersection of the pre-transition baseline with the extrapolated leading edge of the transition".

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

When used herein the terms relating to hygroscopicity are used in accordance with known criteria as set out in J C Callahan et al., Drug Development and Industrial Pharmacy, 1982, 8(3), 355-69 which classifies hygroscopicity with respect to the % weight gain of a test compound under controlled conditions of temperature and humidity (25° C and 75% relative humidity) wherein the test compound has been allowed to attain an approximately constant weight: the following classification is used:

% Weight Gain	Classification
<2%	non-hygroscopic
2-10%	slightly hygroscopic
10-20%	moderately hygroscopic
>20%	very hygroscopic

For the avoidance of doubt when used herein the terms "non-hygroscopic", "slightly hygroscopic", "moderately hygroscopic" and "very hygroscopic" are to have the meanings defined by the above mentioned criteria.

Furthermore, the term "slightly hygroscopic" can particularly mean a compound showing a % weight gain under the above mentioned criteria of any one of 2-9%, 2-8%, 2-7%, 2-6%, 2 –5%, 2-4% and 2-3%.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

"Diabetes mellitus" preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of

Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides the Sodium Salt thereof for use as an active therapeutic substance.

More particularly, the present invention provides the Sodium Salt for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Sodium Salt may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. Suitable methods for formulating the Sodium Salt are generally those disclosed for Compound (I) in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Sodium Salt and a pharmaceutically acceptable carrier therefor.

The Sodium Salt is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the

active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Sodium Salt or a solvate thereof to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of Sodium Salt for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Sodium Salt or a solvate thereof may be taken in amounts so as to provide Compound (I) in suitable doses, such as those disclosed in EP 0,306,228, WO94/05659 or WO98/55122.

The unit dose compositions of the invention comprise the Sodium Salt or a pharmaceutically acceptable solvate thereof in an amount providing up to 12mg, including 1-12mg such as 2-12mg of Compound (I), especially 2-4mg, 4-8mg or 8-12mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12mg of Compound (I). Thus in particular there is provided a pharmaceutical composition comprising the Sodium Salt or a pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier therefor, wherein the Sodium Salt or a pharmaceutically acceptable solvate thereof is present in an amount providing 1, 2, 4, 8, 12, 4 to 8 or 8 to 12mg of Compound (I); such as 1mg of Compound (I); such as 2mg of Compound (I); such as 4mg of Compound (I); such as 8mg of Compound (I); such as 12mg of Compound (I).

The invention also provides a pharmaceutical composition comprising the Sodium Salt or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents and optionally a pharmaceutically acceptable carrier therefor.

The invention also provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Sodium Salt or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents.

In a further aspect the present invention provides the use of the Sodium Salt or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the above mentioned treatments the administration of the Sodium Salt or a pharmaceutically acceptable solvate thereof and the other anti-diabetic agent or agents includes co-administration or sequential administration of the active agents.

Suitably in the above mentioned compositions, including unit doses, or treatments the Sodium Salt or a pharmaceutically acceptable solvate thereof is present in an amount providing up to 12mg, including 1-12mg, such as 2-12mg of Compound (I), especially 2-4mg, 4-8mg or 8-12mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or

12mg of Compound (I) or 4 to 8 or 8 to 12 mg of Compound (I). Thus for example in the above mentioned compositions, including unit doses, or treatments the Sodium Salt or a pharmaceutically acceptable solvate thereof is present in an amount providing 1mg of Compound (I); the Sodium Salt or a pharmaceutically acceptable solvate thereof is present in an amount providing 2mg of Compound (I); the Sodium Salt or a pharmaceutically acceptable solvate thereof is present in an amount providing 3mg of Compound (I); the Sodium Salt or a pharmaceutically acceptable solvate thereof is present in an amount providing 4mg of Compound (I); or the Sodium Salt or a pharmaceutically acceptable solvate thereof is present in an amount providing 8mg of Compound (I).

The other antidiabetic agents are suitably selected from biguanides, sulphonylureas and alpha glucosidase inhibitors. The other antidiabetic agent is suitably a biguanide. The other antidiabetic agent is suitably a sulphonylurea. The other antidiabetic agent is suitably an alpha glucosidase inhibitor. Suitable antidiabetic agents are those disclosed in WO98/57649, WO98/57634, WO98/57635, WO98/57636, WO99/03477, WO99/03476.

The contents of the above mentioned publications are incorporated herein by reference.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following examples illustrate the invention but do not limit it in any way.

Examples

Example 1 5-[4-[2-(*N*-Methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt

A solution of sodium hydroxide (0.40 g) in water (5 ml) was added to a stirred solution of 5-[4-[2-(*N*-methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (3.0 g) in tetrahydrofuran (THF, 30 ml) at 50°C. The clear solution was cooled to 21°C over approximately 1 hour and the solvent evaporated under reduced pressure to give 5-[4-[2-(*N*-methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt (3.2 g) as a crystalline solid.

Example 2 5-[4-[2-(*N*-Methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt

A stirred suspension of 5-[4-[2-(*N*-methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione (3.0 g) in propan-2-ol (30 ml) was heated to 60°C before a solution of sodium hydroxide (0.40 g) in water (5 ml) was added. The stirred mixture was heated to reflux to give a clear solution and was then cooled to 21°C over approximately 1 hour. The solid precipitate was collected by filtration, washed with propan-2-ol (10 ml) and dried under vacuum at 50°C for 2 hours to yield the 5-[4-[2-(*N*-methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt (2.09 g) as a white, crystalline solid.

Found: C: 56.82, H: 4.73, N: 10.95; Expect C: 56.97, H: 4.78, N: 11.08.

^{1}H-NMR (d_6-DMSO): Consistent with the 5-[4-[2-(*N*-methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt.

Example 3 5-[4-[2-(*N*-Methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt

A solution of sodium hydroxide (3.36 g) in water (10 ml) was added to a stirred suspension of 5-[4-[2-(*N*-methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (25.0 g) in propan-2-ol (250 ml) at reflux. The stirred mixture was maintained at reflux for 15 minutes and then cooled to 21°C over approximately 1 hour. The white solid was collected by filtration, washed with propan-2-ol (2x50 ml) and dried under vacuum over phosphorus pentoxide for 16 hours to afford the 5-[4-[2-(*N*-methyl-*N*-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, sodium salt (24.83 g) as a white, crystalline solid.

Characterising data recorded for the product of Example 2

The infrared absorption spectrum of a mineral oil dispersion of the product was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution (Figure 1). Data were digitised at 1 cm^{-1}intervals. Bands were observed at: 1664, 1595, 1566, 1547, 1504, 1462,

1423, 1325, 1271, 1238, 1198, 1179, 1152, 1059, 1008, 977, 928, 816, 784, 765, 741, 729, 721, 556, 520 cm^{-1}.

The infrared spectrum of the solid product was recorded using a Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a universal ATR accessory. Bands were observed at: 3059, 3032, 3010, 2940, 2872, 1663, 1593, 1560, 1546, 1502, 1463, 1422, 1369, 1323, 1270, 1227, 1198, 1179, 1152, 1112, 1059, 1008, 977, 958, 926, 889, 837, 816, 783, 764, 741, 729, 720, 691, 681 cm^{-1}.

The Raman spectrum (Figure 2) was recorded with the sample in an NMR tube using a Nicolet 960 E.S.P. FT-Raman spectrometer, at 4 cm^{-1} resolution with excitation from a Nd:V04 laser (1064 nm) with a power output of 400mW. Bands were observed at: 3060, 3011, 2942, 2914, 2872, 1686, 1674, 1608, 1595, 1583, 1558, 1464, 1450, 1433, 1425, 1413, 1387, 1317, 1276, 1232, 1210, 1180, 1097, 1054, 1009, 979, 924, 890, 848, 831, 785, 749, 682, 642, 625, 521, 484, 403, 338 cm^{-1}.

The X-Ray Powder Diffractogram pattern of the product (Figure 3) was recorded using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator current: 40 mA, Start angle: 2.0 °2θ, End angle: 35.0 °2θ, Step size: 0.02 °2θ , Time per step: 2.5 seconds.Characteristic XRPD angles and relative intensities are recorded in Table 1.

Table 1

Angle	Rel. Intensity
2-Theta °	**%**
3.3	50.7
6.6	22.8
9.9	100
12.2	0.6
15.3	4.5
16.5	22.9
16.9	11.8
17.3	8.1
18.4	16.9
18.8	9.3
19.9	67.5
20.4	4.7
20.9	5.7
21.0	5.9
22.0	2.2
23.0	37.6
24.1	5.7
25.1	6.4

25.7	22.2
26.5	3.9
27.4	6.6
28.5	5.5
29.4	4.2
30.0	18.6
30.7	13.6
31.4	7
31.6	5.6
33.0	33.9
34.3	6.9

The solid-state NMR spectrum of the Sodium Salt (Figure 4) was recorded on a Bruker AMX360 instrument operating at 90.55 MHz: The solid was packed into a 4 mm zirconia MAS rotor fitted with a Kel-F cap and rotor spun at ca.10 kHz. The ^{13}C MAS spectrum was acquired by cross-polarisation from Hartmann-Hahn matched protons (CP contact time 3 ms, repetition time 15 s) and protons were decoupled during acquisition using a two-pulse phase modulated (TPPM) composite sequence. Chemical shifts were externally referenced to the carboxylate signal of glycine at 176.4 ppm relative to TMS and were observed at: 37.2, 41.4, 51.1, 62.7, 68.9, 102.9, 109.8, 112.1, 119.2, 130.7, 132.1, 132.9, 138.5, 148.9, 159.5, 191.6, 197.7 ppm.

Properties of the Sodium Salt

Melting Point of the Sodium Salt recorded for the product of Example 3

The melting point of the Sodium Salt was determined according to the method described in the U.S. Pharmacopoeia, USP 23, 1995, <741> "Melting range or temperature, Procedure for Class Ia", using a Buchi 545 melting point instrument.

Sample was observed to discolour above 200°C. A brown solid was formed by 230°C. Melting point of the brown solid: 246°C.

T_{onset} of the Sodium Salt recorded for the product of Example 2

The T_{onset} of the drug substance was determined by Differential Scanning Calorimetry using a Perkin-Elmer DSC 7 apparatus.

T_{onset} (10°C/minute, closed pan): 155°C, 249°C.